Pending claims

Claims 1 to 29 are pending. Claims 1-7, 17-27 and 29 are canceled, claims 30-34 are added, claims 8-16 and 28 are amended. Upon entry of this Amendment and Response, claims 8-16, 28, and 30-34 are presented for examination. No new matter is added by this amendment. Support for the amended is found throughout the specification and claims as originally filed.

The present invention relates to a gene which is involved in the control of obesity and fertility. In particular the sequences described in the present invention are involved in late onset obesity in males. Thus, the present invention relates to a nucleic acid molecule encoding a 5'OT-EST polypeptide, vectors comprising the nucleic acid molecule, and host cells comprising the vector. The invention further relates to a method of producing a 5'OT-EST wherein the vector comprising the nucleic acid molecules of the invention is used to transform a host cell, and wherein the host cell is then cultured so as to produce the 5'OT-EST polypeptide.

Formal Matters

Oath/Declaration

The Examiner has objected to the Declaration as being defective due to non-initialed or non-dated alterations. The Examiner has also objected to the Declaration as incorrectly citing the priority for which the present application seeks benefit. A substitute Declaration is submitted to herewith. The substitute Declaration makes clear that the present application claims priority under 35 U.S.C. §120 to PCT application number PCT/GB99/02658, filed August 12, 1999, which claims priority to both GB 9817566.4, filed August 12, 1998, and GB 9910522.3, filed May 6, 1999. Applicants wish to point out that the filing date of the PCT application was noted in the filing papers and the originally filed Declaration as being August 12, 1998, but is in fact August 12, 1999. This has been corrected in the substitute Declaration.

Priority

The Examiner has objected to Applicants' claim for priority as being improper. Applicants submit that, as described above, a substitute Declaration is submitted herewith to correct Applicants' claim for priority. Applicants further submit that a certified copy of application number PCT/GB99/02658 has been requested, and will be submitted as soon as possible.

Specification

The Examiner has objected to the specification for containing references to a URL, as being in inappropriate incorporation of subject matter. Applicants submit that the specification has been amended so as to eliminate the URL references and replace them with the corresponding literature citations. The literature citations added by this amendment do not constitute new matter, as they form the basis for the information referred to by the originally filed URL references.

Claim Objections

The Examiner has objected to claims 8-16 as being dependent on non-elected claims, and for being in improper multiple dependent form. Applicants submit that the claims have been amended to remove the dependency on non-elected claims, and to place the relevant claims in proper multiple dependent form.

Rejection of Claims 8-16 and 28 Under 35 U.S.C. § 112 First Paragraph

Claims 8-16 and 28 were rejected under 35 U.S.C. § 112 First Paragraph for lack of written description. The Examiner asserts that, while the specifically recited polynucleotide and polypeptide sequences meet the written description requirement, substantially homologous sequences, and equivalents thereof do not.

Applicants submit that the claims have been amended to eliminate the recitation of "substantially homologous" sequences, or sequences which hybridize to the recited SEQ ID Nos. The claims, as amended, recite specific SEQ ID Nos and sequences which are "at least 90% homologous to said sequences". Applicants submit that the recitation of the specific sequences by SEQ ID NO. combined with the teachings provided in the specification which describe how to determine sequence homology (see pages 10-12) would convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the claimed invention. Applicants submit that the Examiner's assertion that Applicants have not described any species of the claimed genus with particularity, and that an artisan cannot define the metes and bounds of what is encompassed by substantially homologous sequences are moot in view of the present claim amendments.

Rejection of Claims 8-16 and 28 Under 35 U.S.C. § 112 Second Paragraph

Claims 8-16 were rejected as being dependent on non-elected claims, and for being unclear in the recitation of 'claims 1-7 claim **X**'. Applicants submit that this rejection is moot in view of the presently amended claims, and request that the rejection be reconsidered and withdrawn.

Claims 9 and 10 were rejected as being indefinite, because the metes and bounds encompassed by "substantially homologous" is not defined. Applicants submit that claims 9 and 10 have been amended to specifically recite 90% homology, and that this rejection is now moot. Applicants request that this rejection be reconsidered and withdrawn.

Claims 9 and 10 were rejected as being unclear. The Examiner states that the claim recites base pairs of SEQ ID Nos. 5, 7, and 16, but that these sequences are polypeptide sequences. Applicants submit that they have reviewed the sequence listing filed in the present application, and that SEQ ID Nos. 5, 7, and 16 are, in fact, polynucleotide sequences. Applicants request that this rejection be withdrawn.

Claims 12-16 were rejected as unclear because they recite a vector of any one of claims 1-7 (claims 1-7 are now incorporated into the claims which depended from them), but claims 1-7 are drawn to polypeptide sequences. Applicants submit that claims 12-16 have been amended to depend from claims 8 to 10 which recite nucleic acid molecules. Applicants further submit that the claims 13-16 have been amended to correctly recite the claims from which they depend. Applicants request that the rejection be reconsidered and withdrawn.

Claim 13 was rejected as being unclear in the recitation of the TO, AVP and hGH genes because the metes and bounds encompassed by "gene" is unclear. Applicants submit that the claim has been amended to recite "the coding region of the" TO, AVP, or hGH gene. Applicants submit that the claim, as amended, is clear with respect to what is encompassed by the recited sequences.

Claim 28 has been rejected as being vague and unclear because it is drawn to a diagnostic reagent. The Examiner asserts that the specification fails to provide a clear guidance to what the reagent may be. Applicants respectfully disagree with the Examiner. The specification teaches on page 30, lines 31-39 that:

> In another embodiment, the information disclosed herein will enable those skilled in the art to design nucleotide probes for, or develop polyclonal or monoclonal antibodies against, the DNA, RNA or protein sequences corresponding to the whole or parts fo the 5'OT-EST gene in other animals of commercial importance, or more preferably, humans. These are of value in diagnostic tests to screen for mutations in this gene in animal or human populations subject to variations in obesity or fertility. They may also be used to monitor the development, progression, amelioration or cure of obesity or infertility as may be reflected in changes in the activity of this gene or its products. Such predictive tests are recognized to have beneficial value when applied to the human population (Whitaker et al., 1997).

The specification further teaches on page 30, line 40 to page 31, line 2 that:

> Examples of such probes or peptides or proteins used to develop

> antibodies include those predicted form the wild-type and mutated sequences in the rat 5'OT-EST gene and mutants thereof, as well as their derivatives as described above, as well as those that may be inferred from homologous genes in human and mouse, either as intact sequences or formed in whole or in part as fusion sequences with other proteins to facilitate production or purification by standard methods known to those skilled in the art.

Moreover, the specification teaches on page 44, line 25 to page 45, line 4, the use of specific probes (set forth in SEQ ID Nos 14 and 15) for the detection of 5'OT-EST nucleic acid sequences.

Applicants therefore submit that the specification teaches both nucleic acid and antibody probes which function as diagnostic reagents for detecting changes in the 5'OT-EST sequence, or expression thereof which may predispose an individual to obesity. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 8-12, 15-16, and 28 Under 35 U.S.C. § 102(b)

Claims 8-12, 15-16, and 28 were rejected under 35 U.S.C. § 102 (b) as being anticipated by GenBank sequence entries AA955566, AA421393, AA505752, AA421310, AA2422211, AA24389, AA104180, AA850004, H31115, and H31114. The Examiner states that each of the GenBank sequence entries encodes a polypeptide which shares homology to the instantly claimed 5'OT-EST. Applicants submit that the claims have been amended to recite the polynucleotide sequences of SEQ ID Nos. 2, 4, or 6 or a polynucleotide sequence at lease 90% homologous thereto, thus rendering the rejection moot.

Applicants submit that the shortest amino acid sequence of SEQ ID Nos. 2, 4, or 6 is 200 amino acids long (SEQ ID Nos. 2 and 6). Thus, for a prior art sequence to be at least 90% homologous to one or more of these recited SEQ ID Nos. the prior art amino acid sequence must be at least 180 amino acids long. Of the GenBank sequences cited above, the longest sequence is 582 nucleotides in length (AA245389), which could maximally encode a 194 amino acid

sequence. However, Applicants have translated this nucleotide sequence using the translate tool available at http://www.expasy.ch/tools/dna.html. The translation returned the following possible reading frames:

5'3' Frame 1
N S D P T S G G E C R A W S D **Stop** G C S G N G **Stop** A I L L G C T N S Y P S T Q T L G
K H C A Y L G P Q K S L C S V P D H L P F F G D G P V V T L R R V Q R F F Y P C L Q V
L P S D E V F C L L L Q L E H F L L F Q L H P S L L L L S P L A L G L S L L H L L G L C F
Q L Q P R Y P **Stop** L L H S P V L V P V P G H Q L P V L R E W L L R L A T A R T P A W
A S C N F L S H V N V N S S L R A R

5'3' Frame 2
I R I Q R Q V V S A E P G V T E V A L E T A E P S S W D V P I P I P V H R P **Stop** A S T V
L I W A P R S L C A Q F L T T C P S L V T A Q L **Stop** L F G E S N A S S I R A S R F S R V
Met K F F A S S C S L S T S C S F S C T Q A C S S **Stop** A L W R W A S A F C T S W A C
A S S C N L A I R S S C I R R F S S R F Q A I S S R C S V N G C C A L L R P E P R L G P R
A I S F R T S T **Stop** T L A **Stop** E R A

5'3' Frame 3
F G S N V R W **Stop** V P S L E **Stop** L R L L W K R L S H P P G **Met** Y Q F L S Q Y T D P R
Q A L C L F G P P E V S V L S S **Stop** P P A L L W **Stop** R P S C N S S E S P T L L L S V P P
G S P E **Stop Stop** S F L P P P A A **Stop** A L L A L S V A P K P A P P E P S G A G P Q P S A
P P G P V L P A A T S L S V A P A F A G S R P G S R P S A P G A P **Stop Met** A A A P C Y
G Q N P G L G L V Q F P F A R Q R E L **Stop** P E S A

3'5' Frame 1
C A L S G **Stop** S S R **Stop** R A K G N C T R P K P G F W P **Stop** Q G A A A I H G A P G A
D G L E P G R E P A N A G A T D S E V A A G S T G P G G A E G **Stop** G P A P E G S G G
A G L G A T E R A R S A Q A A G G G K K L H H S G E P G G T D R R S V G L S E E L Q
L G R H Q R R A G G Q E L S T E T S G G P N K H S A C L G S V Y W D R N W Y I P G G
W L S R F Q S N L S H S R L G T H H L T L D P N
3'5' Frame 2
A R S Q A R V H V D V R K E I A R G P S R G S G R S K A Q Q P F T E H R E L **Met** A W
N R D E N R R **Met** Q E L R I A R L Q L E A Q A Q E V Q K A E A Q R Q R A Q E E Q A W
V Q L K E Q E V L K L Q E E A K N F I T R E N L E A R I E E A L D S P K S Y N W A V T
K E G Q V V R N **Stop** A Q R L L G A Q I S T V L A **Stop** G L C T G I G I G T S Q E D G S
A V S R A T S V T P G S A L T T **Stop** R W I R I

3'5' Frame 3

R A L R L E F T L T C E R K L H E A Q A G V L A V A R R S S H S R S T G S **Stop** W P G
T G T R T G E C R S Y G **Stop** R G C S W K H R P R R C R R L R P S A R G L R R S R L G
C N **Stop** K S K K C S S C R R R Q K T S S L G R T W R H G **Stop** K K R W T L R R V T T
G P S P K K G R W S G T E H R D F W G P K **Stop** A Q C L P R V C V L G **Stop** E L V H P
R R **Met** A Q P F P E Q P Q S L Q A R H S P P D V G S E

As can be seen, the longest amino acid sequence which could be encoded by this nucleotide sequence, when taking into account the presence of stop codons, is 112 amino acids in length, and thus cannot comprise a sequence which is at least 90% identical to any one of SEQ ID Nos. 2, 4, or 6. The next longest GenBank sequence is 521 nucleotides long, which can maximally encode a 170 residue amino acid sequence, and thus cannot comprise a sequence which is at least 90% identical to any one of SEQ ID Nos. 2, 4, or 6.

Applicants therefore submit that none of the GenBank sequences cited by the Examiner can encode an amino acid sequence which comprises a sequence which is at least 90% identical to the sequences recited in the claims as amended. Accordingly, Applicants request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicant(s) submit(s) that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date: 2/20/02

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Marked-up Version of Amendments:

1.

Cross Reference to Related Applications

This application claims priority under 35 U.S.C. §120 to International Application serial number PCT/GB99/02658, filed August 12, 1999, which claims priority to application serial number GB9910522.3, filed May 6, 1999, and GB9817566.4, filed August 12, 1998, all of which are incorporated herein in their entirety.

2.

Sequence homology (or identity) may moreover be determined using any suitable homology algorithm, using for example default parameters. Advantageously, the BLAST algorithm is employed, with parameters set to default values. The BLAST algorithm[described in detail at http://www.ncbi.nih.gov/BLAST/blast_help.html, which is incorporated herein by reference.] is known to those of skill in the art and is described, for example, in Altschul et al., 1990 (*J. Mol. Biol.* 215: 403). [The search parameters are defined as follows, and are advantageously set to the defined default parameters.]

3.

BLAST (Basic Local Alignment Search Tool) is the heuristic search algorithm employed by te programs blastp, blastn, blastx, tblastn, and tblastx; these programs ascribe significance to their findings using the statistical methods of Karlin and Altschul (see [http://www.ncbi.nih.gov/BLAST/blast_help.html] Altschul et al., 1990 *J. Mol. Biol.* 215: 403) with a few enhancements. The BLAST programs were tailored for sequence similarity searching, for example to identify homologues to a query sequence. The programs are not generally useful for motif-style searching. For a discussion of basic issues in similarity searching of sequence databases, see Altschul et al. (1994).

4.

More preferably, sequence comparisons are conducted using the simple BLAST search algorithm (Altschul et al., 1990 *J. Mol. Biol.* 215: 403) [provided at http://www.ncbi.nih.gov/BLAST].

In the Claims

8. (Amended) A nucleic acid encoding a 5'OT-EST polypeptide [or mutant 5'OT-EST,] wherein said polypeptide comprises a sequence selected from the group consisting of the sequences set forth in any one of [claims 1-7] SEQ ID Nos. 2, 4, or 6, and sequences which are at least 90% homologous to said sequences set forth in any one of SEQ ID Nos. 2, 4, or 6.

9. (Amended) [A] The nucleic acid of [any one of claims 1-7] claim 8, having a sequence selected from the group consisting of [any one of] SEQ. ID. Nos. 1, 3, 5, 7, 16 or 17, [sequences] or a sequence which [are hybridisable under stringent conditions with an oligonucleotide comprising 20 contiguous based form any one of SEQ ID Nos. 1, 3, 5, 7, 16, or 17; sequences substantially] at least 90% homologous to [any one of] SEQ ID Nos. 1, 3, 5, 7, 16, or 17 [and sequences complementary thereto].

10. (Amended) [A] The nucleic acid of [any one of claims 1-7] claim 9, comprising the sequence
ATGTTGCGGGCTTTGAACCGCCTGGCCGCGCGGCCCGGGGGCCAGCCCCCAACCCT
GCTCCTTCTGCCCGTGCGCGGCCCACGGCCCCGCTCATTCTCGGCTCCTTTTTCCTCG
CAGGATAGC, or an equivalent sequence which encodes the same polypeptide having regard to the degeneracy of the nucleic acid code, or a sequence [substantially] at least 90% homologous thereto.

11. (Amended) A nucleic acid vector comprising a nucleic acid sequence of any one of claims 8 to 1[1]0.

12. (Amended) [A] The vector of [any one of claims 1-7] claim 11 [which], wherein said vector is a cosmid vector.

13. (Amended) [A] The vector of [any one of claims 1-7]claim 11 or 12 further comprising one or more sequences selected from the group consisting of sequences of the coding region of the oxytocin (OT) gene, the coding region of the vasopressin (AVP) gene, or the coding region of the human growth hormone (hGH) gene.

14. (Amended) A vector of [any one of claims 1-7] claim 12, wherein said vector has the structure of cVO14 as set forth in Figure 4 (SEQ. ID. No. 17).

15. (Amended) A cell transformed with a vector of any one of claims [1-7 any one of claims] 11 to 1[3]4.

16. (Amended) A method for producing a 5'OT-EST polypeptide [or] having a [mutant 5'OT-EST polypeptide] sequence selected from the group consisting of the sequences set forth in any one of [claims 1-7 any one of claims 1] SEQ ID Nos. 2, 4, 6, or sequences which are at least 90% homologous to [7,] said sequences set forth in any one of SEQ ID Nos. 2, 4, or 6, comprising transforming a cell with a vector of any one of claims [1-7 any one of claims] 11 to 1[3]4 and culturing the cell to produce the polypeptide.

28. (Amended) A diagnostic reagent for the detection of mutations, polymorphisms or other changes in *5'OT-EST* which may predispose an individual to obesity, comprising at least one detectably labeled nucleic acid probe which is capable of hybridizing to *5'OT-EST* or a sequence at least 90% homologous to *5'OT-EST.*

Please **add** claims 30-34

30. (New) The nucleic acid of claim 8, wherein said 5'OT-EST polypeptide comprises an amino acid sequence encoded by at least one exon selected from the group consisting of exons w, x, y, or z as set forth in SEQ ID No. 16.

31. (New) The nucleic acid of claim 8, wherein said 5'OT-EST polypeptide is a mutant 5'OT-EST polypeptide which, *in vivo*, modulates the obesity of an animal which expresses said mutant 5'OT-EST polypeptide.

32. (New) The nucleic acid of claim 30, wherein said animal which expresses said mutant 5'OT-EST polypeptide is a transgenic animal comprising a transgene encoding said mutant 5'OT-EST polyepeptide.

33. (New) The nucleic acid of any one of claims 8, 29, 30, or 31 wherein said 5'OT-EST polypeptide comprises the sequence PRPRSFSAPFSQDS.

34. (New) The nucleic acid of any one of claims 8, 29, 30, or 31 wherein said 5'OT-EST polypeptide comprises the sequence MLRALNRLAARPGGQPPTLLLLPVRGPRPRSFSAPFSSQDS.